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IBM Technical Disclosure Bulletins

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DATE: Tuesday, September 02, 2003 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
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L18	L17 with l11	1100	L18
L17	lysing or lytic or cyto$	147187	L17
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L11	ethanol	314350	L11
L10	l9 same l4	7	L10
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L8	ethanol or endosomolytic	314405	L8
L7	l4 and l3	19	L7
L6	l4 same l3	0	L6
L5	l4 with l3	0	L5
L4	endocytosis or endosome or endosomo$ or lysomotro$	7278	L4
L3	L2 with l1	2802	L3
L2	nanoparticle or polymer or microparticle	1516641	L2
L1	ortho-ester or hydrazine or hydrazone or cis-actonyl	66662	L1

END OF SEARCH HISTORY

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L7: Entry 2 of 19 File: PGPB Feb 6, 2003

PGPUB-DOCUMENT-NUMBER: 20030026841
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030026841 A1

TITLE: Compositions and methods for drug delivery using pH sensitive molecules

PUBLICATION-DATE: February 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Hagstrom, James E.	Middleton	WI	US	
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Rozema, David B.	Madison	WI	US	
Monahan, Sean D.	Madison	WI	US	

US-CL-CURRENT: 424/486; 514/2, 514/44, 514/54, 514/56, 514/59

CLAIMS:

We claim:

1. The process for delivery of a polyion to a cell, comprising: a) forming a complex of labile polyampholyte and polyion; and, b) delivering the complex into a cell.

2. The process of claim 1 wherein the labile bond is a pH labile bond.

3. The process of claim 2 wherin the pH-labile bond is selected from the group consisting of acetal, ketal, silazane, silyl ether, ortho ester, enol ether, enol ester, imine, amidine, imidate ester, substructure of citraconic anhydride, and substructure of maleic anhydride.

4. The process of claim 1 wherein the polyampholyte comprises one or more polycations selected from the group consisting of poly-L-lysine, poly-D-lysine, poly-L,D-lysine, polyethylenimine, polyallylamine, poly-L-omithine, poly-D-ornithine, poly-L,D-ornithine, polyvinylamine, natural cationic proteins, synthetic cationic proteins, synthetic cationic peptides and synthetic polymers.

5. The process of claim 4 wherein the synthetic polymers consist of monomers with amines selected from the group consisting of alkylamine, aryl amine, aralkylamine, imidazole, pyridine, and piperazine, pyrazine , pyrimidine, oxazoline, and oxazole.

6. The process of claim 1 wherin the polyampholyte comprises one or more polyanions selected from the group consisting of to poly-L-aspartic acid, poly-D-aspartic acid, poly-L,D-aspartic acid, polyacrylic acid, poly-L-glutamic acid, poly-D-glutamic acid, poly-L,D-glutamic acid, succinylated poly-L-lysine, succinylated poly-D-lysine, succinylated poly-L,D-lysine, succinylated polyethylenimine, succinylated polyallylamine, succinylated poly-L-ornithine, succinylated poly-D-omithine, succinylated poly-L,D-omithine, succinylated polyvinylamine, polymethacrylic acid, dextran sulfate, heparin, hyaluronic acid, DNA, RNA, natural anionic proteins, synthetic anionic proteins, synthetic anionic peptides, and synthetic polymers

contining monomers in which an amine has been reacted with a substructure of citraconic anhydride and/or substructure of maleic anhydride.

7. The process of claim 1 wherein the polyampholyte contains a functional group.

8. The process of claim 7 wherein the functional group on the polyampholyte undergoes a chemical reaction.

9. The process for delivery of a polyion to a cell, comprising: a) forming a complex of a polyion and a polyampholyte having a pH labile bond; and, b) delivering the complex into a cell.

10. The process of claim 9 wherein the pH-labile bond is selected from the group consisting of acetal, ketal, silazane, silyl ether, ortho ester, enol ether, enol ester, imine, amidine, imidate ester, substructure of citraconic anhydride, and substructure of maleic anhydride.

11. The process of claim 9 wherein the polyampholyte comprises one or more polycations selected from the group of poly-L-lysine, poly-D-lysine, poly-L,D-lysine, polyethylenimine, polyallylamine, poly-L-omithine, poly-D-omithine, poly-L,D-omithine, polyvinylamine, natural cationic proteins, synthetic cationic proteins, synthetic cationic peptides and synthetic polymers.

12. The process of claim 11 wherein the synthetic polymers contain monomers with amines selected from the group consisting of alkylamine, aryl amine, aralkylamine, imidazole, pyridine, and piperazine, pyrazine , pyrimidine, oxazoline, oxazole.

13. The process of claim 9 wherin the polyampholyte comprises one or more polyanions selected from the group consisting of poly-L-aspartic acid, poly-D-aspartic acid, poly-L,D-aspartic acid, polyacrylic acid, poly-L-glutamic acid, poly-D-glutamic acid, poly-L,D-glutamic acid, succinylated poly-L-lysine, succinylated poly-D-lysine, succinylated poly-L,D-lysine, succinylated polyethylenimine, succinylated polyallylamine, succinylated poly-L-ornithine, succinylated poly-D-ornithine, succinylated poly-L,D-omithine, succinylated polyvinylamine, polymethacrylic acid, dextran sulfate, heparin, hyaluronic acid, DNA, RNA, natural anionic proteins, synthetic anionic proteins, synthetic anionic peptides, and synthetic polymers contining monomers in which an amine has been reacted with a substructure of citraconic anhydride and/or substructure of maleic anhydride.

14. The process of claim 9 wherein the polyampholyte contains a functional group.

15. The process of claim 14 wherein the functional group on the polyapmpholyte undergoes a chemical reaction.

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L7: Entry 16 of 19 File: USPT Jun 9, 1998

DOCUMENT-IDENTIFIER: US 5762918 A
TITLE: Methods of using steroid-polyanionic polymer-based conjugated targeted to vascular endothelial cells

Detailed Description Text (22):
Typical acid-labile linkages believed to be useful in connection with the present invention include those that employ a Schiff's base linkage, for example, linkages incorporating the condensation product of an aldehyde or ketone with a hydrazine, a hydrazide, a primary or secondary amine or their derivatives. A particularly preferred Schiff's base linkage for use in accordance herewith is an acyl hydrazone bond, formed when a hydrazide derivative of heparin, or other polyanionic compound or polymer, is condensed with a selected agent containing a ketone or aldehyde group. It is proposed that the heparin or other polyanionic compound or polymer can be derivatised to introduce hydrazide-terminating side chains of various lengths. The simplest hydrazide-terminating side chain contemplated has the structure:

Detailed Description Text (88):
In designing an acid-labile bond, it is reasoned that the endocytosis of the conjugate by the endothelial cell would result in its delivery to acidified endosomes and lysosomes. This is known to occur with heparin itself (Fabian et al., 1978; Barzu et al., 1985). The presence of the acid-labile bond would then allow the release of the selected agent from such acid intracellular compartments. The selected agents, such as steroids, would then be free to exert their effects only when inside the target cells, and would be otherwise maintained in an active state whilst circulating in the body.

Detailed Description Text (95):
The heparin-cortisol conjugate was constructed by first condensing the carboxyl groups of accessible glucuronic acid and iduronic acid residues in heparin with adipic dihydrazide. This resulted in the introduction of hydrazide groups into heparin which, on mixing with cortisol, condensed with the ketone group on C3 of the steroid to form a conjugate in which the heparin and the steroid were joined by an acyl hydrazone bond. This bond was stable at pH 7.4 but, as required, allowed the rapid dissociation of the conjugate at pH 4.8. The first destination of the conjugate following internalization would be the acidified endosomes and lysosomes, which, with a pH of .about.4.8, would promote the rapid release of the steroid.

Detailed Description Text (167):
These results demonstrate that the acyl hydrazone bond joining the two components of the conjugate was markedly acid-labile, as expected. Uptake of heparin-cortisol by endothelial cells and delivery of the conjugate to acidified endosomes and lysosomes would thus be expected to lead to the rapid release of the steroid since these intracellular compartments have a pH of approximately 4.8.

Other Reference Publication (9):
Pino, "Binding and Endocytosis of Heparin-Gold Conjugates by the Fenestrated Endothelium of the Rat Choriocapillaris," Cell Tissue Research, 250:257-266, 1987.

Other Reference Publication (12):
Barzu et al., "Binding and Endocytosis of Heparin by Human Endothelial Cells in Culture," Biochimica et Biohpysica Acta, 845:196-203, 1985.

CLAIMS:

13. The method of claim 12, wherein said polymer is derivatized to introduce side chains terminating in hydrazide, hydrazine, primary amine or secondary amine groups.

14. The method of claim 13, wherein the derivatized polymer is the condensation product of the polymer and adipic dihydrazide, succinic dihydrazide, hydrazine or hydrazine hydrate, and said selected steroidal agent or agents is conjugated to the polymer through a Schiff's base linkage.

15. The method of claim 14, wherein said selected steroidal agent or agents is conjugated to said polymer through a hydrazone or acyl hydrazone bond.

L10: Entry 6 of 7 File: PGPB Jul 5, 2001

DOCUMENT-IDENTIFIER: US 20010006817 A1
TITLE: CELL DELIVERY COMPOSITIONS

Abstract Paragraph (1):
The present invention provides improved cell delivery compositions. In particular, the invention provides biocompatible endosomolytic agents. In a preferred embodiment, the endosomolytic agents are also biodegradable and can be broken down within cells into components that the cells can either reuse or dispose of. Preferred endosomolytic agents include cationic polymers, particularly those comprised of biomolecules, such as histidine, polyhistidine, polylysine or any combination thereof. Other exemplary endosomolytic agents include, but are not limited to, other imidazole containing compounds such as vinylimidazole and histamine. More particularly preferred are those agents having multiple proton acceptor sites and acting as a "proton sponge", disrupting the endosome by osmolytic action. In preferred embodiments, the endosomolytic agent comprises a plurality of proton acceptor sites having pKas within the range of 4 to 7, which endosomal lysing component is polycationic at pH 4. The present invention also contemplates the use of these endosomolytic agents as delivery agents by complexation with the desired compound to be delivered. Thus, the present invention also acts as a cell delivery system comprising an endosomolytic agent, a delivery agent, and a compound to be delivered.

Summary of Invention Paragraph (8):
[0008] The present invention provides improved cell delivery compositions. In particular, the invention provides a biocompatible endosomolytic system. These inventive endosomolytic agents obviate the need for known agents (i.e., chloroquine, fusogenic peptides, inactivated adenoviruses, and polyethyleneimine) that can burst endosomes but have negative effects on cells. Preferred inventive endosomolytic agents are biodegradable in that they are broken down within cells into components that the cells can either reuse or dispose of. Particularly preferred inventive endosomolytic agents are cationic polymers comprised of biomolecules. Although the present invention is not limited by the mechanism of action of the endosomolytic agents, certain preferred agents have multiple proton acceptor sites and would be expected to act as "proton sponges", disrupting the endosome by osmolytic action. Particularly preferred agents are polycationic under the conditions of the endosome (i.e., at pH 4). Exemplary endosomolytic agents include, but are not limited to, imidazole containing compounds such as histidine, histamine, vinylimidazole, polymers thereof, and any combinations thereof.

Summary of Invention Paragraph (9):
[0009] In one preferred embodiment of the invention, the endosomolytic agent comprises polyhistidine. Polyhistidine for use in accordance with the present invention may be provided as a linear or branched polyhistidine polymer. Moreover, as is discussed further below, the polyhistidine may be provided in combination with one or more additional agents. Where such other agents are other polymers, or functionalizable chemical compounds, they may be co-polymerized or functionalized with polyhistidine or histidine. Thus, a polyhistidine endosomolytic agent of the present invention need not comprise a polyhistidine polymer per se, so long as it has a sufficient number of histidine functional groups to preserve poyhistidine functionality as described herein. To give but one example, the inventive endosomolytic agent may comprise a single linear or branched copolymer synthesized from any appropriate combination of polyhistidine, polylysine, histidine, and/or lysine.

Detail Description Paragraph (4):
[0034] As discussed above, the present invention provides an improved system for delivery of compounds to cells and lysis of endosomal cell compartments. In particular, the invention provides biocompatible, preferably biodegradable, endosomolytic agents. While the mechanism of action of the endosomolytic agents is not intended to limit the scope of the present invention, preferred agents have multiple proton acceptor sites (i.e., multiple groups with a pKa intermediate between pH 4 and pH 7) and/or are polycationic, at least when they are within the endosome. Particularly preferred agents are linear or branched polymers of biomolecules, preferably of amino acids or amino acid derivatives. Exemplary endosomolytic agents include, but are not limited to, imidazole containing compounds such as histidine, histamine, vinylimidazole, polymers thereof, and any combinations thereof.

Detail Description Paragraph (7):
[0037] The polyhistidine endosomolytic agent of the present invention may be a linear polymer or a branched polymer. Moreover, the polyhistidine may be combined or polymerized with one or more additional agents with desirable cell delivery attributes. For example, the polyhistidine may be combined with a delivery agent selected to interact with the compound to be delivered to the cell. However, the polyhistidine of the present invention is not combined with chloroquine, fusogenic peptides, inactivated adenoviruses, and polyethyleneimine.

CLAIMS:

83. The method of claim 82, wherein the endosomolytic lysing component comprises a polymer of biomolecules.

L12: Entry 2 of 4 File: USPT Oct 12, 1999

DOCUMENT-IDENTIFIER: US 5965404 A
**** See image for Certificate of Correction ****
TITLE: Method for introducing nucleic acids into higher eukaryotic cells

Abstract Text (1):
Process and medium for the transfection of higher eukaryotic cells with DNA/polycation complexes, wherein a medium is used which contains ethyleneglycol and/or glycerol. The medium may also contain a substance which prevents the acidification of the endosomes, and/or a lower alcohol such as ethanol. The process is particularly suitable for the transfection of primary cells such as fibroblasts. Stably transformed cells can be obtained thereby, e.g. tumour cells for use as tumour vaccines.

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      (FILE 'HOME' ENTERED AT 17:30:19 ON 02 SEP 2003)

      FILE 'MEDLINE, CANCERLIT, CAPLUS, BIOTECHDS, EMBASE' ENTERED AT 17:30:43
      ON 02 SEP 2003
L1        341517 S ETHANOL
L2        178553 S ENDOSOME OR ENDOSOMO? OR LYSOMOTRO? OR LYSIS OR LYTIC OR ENDO
L3          1109 S L2 AND L1
L4        987857 S POLYMER OR MICROPARTICLE
L5            13 S L4 AND L3
L6            11 DUP REM L5 (2 DUPLICATES REMOVED)
L7            26 S L1 AND (ENDOSOME OR ENDOSOMOLYTIC)
L8            16 DUP REM L7 (10 DUPLICATES REMOVED)
L9             0 S L1 AND ENDOSOMOLYTIC
L10            4 S L1 AND LYSING AGENT
L11            3 DUP REM L10 (1 DUPLICATE REMOVED)

=>
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(FILE 'HOME' ENTERED AT 15:28:40 ON 02 SEP 2003)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:29:13 ON 02 SEP 2003

L1	38160	S	ORTHO-ESTER OR HYDRAZONE OR CIS-ACTONYL
L2	1031789	S	NANOPARTICLE OR POLYMER
L3	1414	S	L1 AND L2
L4	3545839	S	PH
L5	216	S	L4 AND L3
L6	176	DUP REM	L5 (40 DUPLICATES REMOVED)
L7	331265	S	ENDOSOME OR CYTOPLASM
L8	0	S	L7 AND L5
L9	168434	S	LYSIS OR LYTIC
L10	0	S	L9 AND L6
L11	289	S	ENDOSOMO?
L12	0	S	L11 AND L6
L13	11756911	S	PHARMACEUTICAL OR THERAP? OR DRUG
L14	58	S	L13 AND L6
L15	35942	S	L1 NOT ORTHO-ESTER
L16	696	S	L15 AND L2
L17	52	S	L16 AND L13
L18	35950	S	HYDRAZONE OR CIS-ACTONYL
L19	696	S	L18 AND L2
L20	660	DUP REM	L19 (36 DUPLICATES REMOVED)
L21	31	S	L20 AND L13
L22	7177	S	L18 AND PH
L23	58333	S	ENDOCYTOSIS
L24	85	S	L23 AND L1
L25	42	DUP REM	L24 (43 DUPLICATES REMOVED)
L26	7350	S	L22 OR LYSOMO?
L27	7231	S	L26 AND L4
L28	121	S	L26 AND L5
L29	109	DUP REM	L28 (12 DUPLICATES REMOVED)
L30	10	S	L29 AND L13

=>

L4 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1993:664187 CAPLUS
DN 119:264187
TI Packaging-defective non-oncoviral vectors based on MPMV and HIV
IN Lever, Andrew Michael Lindsay; Hunter, Eric
PA UK
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9317118	A2	19930902	WO 1993-GB417	19930301
	WO 9317118	A3	19931014		
	W: AU, CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9336394	A1	19930913	AU 1993-36394	19930301
	AU 671101	B2	19960815		
	EP 630409	A1	19941228	EP 1993-905485	19930301
	EP 630409	B1	20021127		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 07504322	T2	19950518	JP 1993-514679	19930301
	EP 1262554	A2	20021204	EP 2002-14431	19930301
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	AT 228569	E	20021215	AT 1993-905485	19930301
	ES 2187504	T3	20030616	ES 1993-905485	19930301
	US 5747307	A	19980505	US 1994-295737	19940826
	US 6294165	B1	20010925	US 1997-994001	19971218
PRAI	GB 1992-4350	A	19920228		
	GB 1992-8489	A	19920416		
	GB 1992-19935	A	19920921		
	EP 1993-905485	A3	19930301		
	WO 1993-GB417	A	19930301		
	US 1994-295737	A1	19940826		

AB A **retrovirus**-based vector is prepd. for expression of heterologous genes for, e.g., gene therapy. The vector is capable of producing viral proteins but not packaging viral RNA. Construction of a vector contg. a deletion corresponding to that between the **primer -binding** site and the 5'-major **splice donor** of Mason-Pfizer Monkey virus (MPMV) was demonstrated. The vector is also lack of the LTR sequence. Prepn. of a vector based on a lentivirus, e.g., HIV-1, was also shown.

L14 ANSWER 54 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1989:199214 CAPLUS
DN 110:199214
TI Method of preparing bioerodible polymers having **pH** sensitivity in the acid range and resulting product and their use in controlled **drug** delivery
IN Heller, Jorge; Penhale, Donald W. H.; Ng, Steve Y.
PA SRI International, USA
SO U.S., 10 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 4764364	A	19880816	US 1986-833215	19860225
US 4855132	A	19890808	US 1988-214452	19880701
PRAI US 1986-833215		19860225		

AB Bioerodible polymers such as poly(ortho esters) I [n >10, R = quadrivalent org. group, R6; R10 = linking group; R11 = quadrivalent org. group; R1 - R4 = H, essentially hydrocarbyl; CHR1R2, CHR3R4 = cyclic; R5 = hydrocarbyl derived from polyol R5(OH)a; a .gtoreq.2] contain amine functionality such that the rate of erosion of the **polymer** in an acidic environment increases as the **pH** diminishes. They are prepd. by copolymn., esp. using II as one of the comonomers. The polymers are useful for controlled **pH**-dependent release of drugs e.g. insulin. The diketene acetal III reacted with N-butyldiethanolamine to form prepolymer II [R1 = R3 = Me, R2 = R4 = H, R = C(CH2)4, R10 = NBu(CH2CH2O)2]. p-Nitroacetanilide was mixed into II at 2 wt.%, the crosslinker 1,2,3-tris(hydroxypropyloxy)propane was added, and the **polymer** was cured as a cylinder 0.25 in diam. at 70 for 18 h. The cylinder was cut into disks which were suspended in buffers at various **pH**'s and the rate of p-nitroacetanilide release was detd. The rate of release was least at **pH** 4.5, greater at **pH** 4.0, and still greater at **pH** 3.5.

L14 ANSWER 43 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:640510 CAPLUS
DN 127:268060
TI **Pharmaceutical** compositions containing buffered **ortho ester** polymers and their preparation
IN Gurny, Robert; Zignani, Monia; Tabatabay, Cyrus
PA Gurny, Robert, Switz.; Zignani, Monia; Tabatabay, Cyrus
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9732606	A1	19970912	WO 1997-EP906	19970226
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, FJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9720934	A1	19970922	AU 1997-20934	19970226
	AU 722303	B2	20000727		
	EP 885014	A1	19981223	EP 1997-906128	19970226
	EP 885014	B1	20021023		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2000506148	T2	20000523	JP 1997-531413	19970226
	AT 226450	E	20021115	AT 1997-906128	19970226
	ES 2185911	T3	20030501	ES 1997-906128	19970226
	US 6440460	B1	20020827	US 1998-117359	19980727
PRAI	EP 1996-103391	A	19960305		
	WO 1997-EP906	W	19970226		

AB The **pharmaceutical** compns. are for the controlled release of **therapeutic** agents from carboxylic acid **ortho ester** polymers. The compn. contains a pharmaceutically acceptable salt of an acid, which together with the carboxylic acid being liberated from the decompn. of the **ortho ester polymer**, forms a buffer system in a physiol. acceptable **pH**-range. In an example, tri-Et orthoacetate was copolymd. with 1,2,6-hexanetriol to give a biodegradable **polymer**. This **polymer** is formulated with NaOAc and 5-fluorouracil and is suitable for an intraocular implant.

L14 ANSWER 40 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:415544 CAPLUS
DN 133:63945
TI Methods and kits for making polypeptides having a single covalently bound N-terminal water-soluble **polymer**
IN Wei, Ziping; Menon-Rudolph, Sunitha; Ghosh-Dastidar, Pradip
PA Ortho-McNeil Pharmaceutical, Inc., USA
SO U.S., 21 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6077939	A	20000620	US 1997-905310	19970804
PRAI US 1997-905310		19970804		

AB This invention provides compns. consisting essentially of a polypeptide and a water-sol. **polymer** covalently bound thereto at the N-terminal .alpha.-carbon atom via a **hydrazone** or reduced **hydrazone** bond, or an oxime or reduced oxime bond. This invention also provides methods of making the instant compns., **pharmaceutical** compns. comprising same, and kits for use in prepg. same.

L14 ANSWER 28 OF 58 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:636513 CAPLUS
TI Poly(ortho esters): Some recent developments
AU Heller, Jorge
CS A. P. Pharma, Redwood City, CA, 94063, USA
SO Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), PMSE-129 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69EKY9
DT Conference; Meeting Abstract
LA English
AB Poly(ortho esters) are best prepd. by the reaction of a diketene acetal with a diol, or mixts. of diols. While these polymers have been under development for over 30 yr, their com. potential has not been realized until a reproducible means of controlling erosion rates could be devised. To do so, we have taken advantage of the acid-sensitive nature of **ortho ester** linkages and incorporated a latent acid catalyst into the **polymer** backbone. The concn. of that segment in the **polymer** backbone controls erosion rates, while the nature of the diols controls mech. and thermal properties. A detailed study of **polymer** erosion has been carried out and an erosion process that occurs predominantly, but not exclusively, in the surface layers has been demonstrated. Such a process has a no. of important consequences such as erosion controlled **drug** release, **drug** release that is concominant with **polymer** erosion and most importantly, the maintenance of an essentially neutral **pH** in the device interior since acidic hydrolysis products can diffuse away from the device. This allows delivery of **pH**-sensitive materials, including DNA.

L14 ANSWER 19 OF 58 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 97289018 EMBASE
DN 1997289018
TI New generation of poly(ortho esters): Synthesis, characterization, kinetics, sterilization and biocompatibility.
AU Zignani M.; Merkli A.; Sintzel M.B.; Bernatchez S.F.; Kloeti W.; Heller J.; Tabatabay C.; Gurny R.
CS R. Gurny, School of Pharmacy, University of Geneva, 30 Quai E. Ansermet, CH-1211 Geneva 4, Switzerland
SO Journal of Controlled Release, (1997) 48/2-3 (115-129).
Refs: 76
ISSN: 0168-3659 CODEN: JCREEC
PUI S 0168-3659(97)00050-3
CY Netherlands
DT Journal; Article
FS 012 Ophthalmology
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB After a brief historical overview of the development of three families of poly(ortho esters) (POEs), the physico-chemical characteristics, **drug** release properties and biocompatibility of the third generation is discussed. Its synthesis is based on a transesterification reaction between 1,2,6-hexanetriol and trimethylorthoacetate. This viscous hydrophobic **polymer** has been used for the sustained release of 5-fluorouracil (5-FU) or mitomycin C (MMC) in glaucoma filtering surgery. It shows a good correlation between **drug** release and **polymer** erosion and can be injected using a hydraulic syringe. **Drug** release can be modulated by using different molecular weights of the **polymer**, or by adding basic or acidic excipients. Because conventional sterilization methods using gamma or electron beam-irradiation can not be used due to changes in molecular weight and dynamic viscosity resulting from backbone cleavage, an aseptic fabrication procedure has been developed and validated. POE biocompatibility has been established after subconjunctival injections of POE, monomers and degradation products in rabbits. Better control of the microenvironmental **pH** during **polymer** degradation has been achieved by using an in situ formed buffer system.

L21 ANSWER 30 OF 31 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1993:76627 CAPLUS
DN 118:76627
TI Hydrazine-containing conjugates of polypeptides and glycopolypeptides with polymers
IN Zalipsky, Samuel; Lee, Chyi; Menon-Rudolph, Sunitha
PA Enzon, Inc., USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9216555	A1	19921001	WO 1992-US2047	19920312
	W: AU, CA, HU, JP, KR, RU				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
	AU 9216769	A1	19921021	AU 1992-16769	19920312
	EP 576589	A1	19940105	EP 1992-909326	19920312
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
	JP 06506217	T2	19940714	JP 1992-508914	19920312
	CA 2101918	AA	19920919	CA 1992-2101918	19920316
PRAI	US 1991-672696		19910318		
	WO 1992-US2047		19920312		

AB Biol. active polypeptides and glycopolypeptides are conjugated at a reactive carbonyl or carboxylic acid group of the polypeptide with water-sol. polymers by a linkage contg. a hydrazide or **hydrazone** functional group. The linkage preferably also includes an amino acid or peptide sequence. The conjugates represent a novel form of **drug** delivery (no data). Methoxy-PEG (mPEG) was treated with phosgene and then reacted with .beta.-alanine Et ester.HCl. The mPEG-.beta.-alanine Et ester product was treated with hydrazine under reflux for 6 h and the mPEG-hydrazide deriv. contg. .beta.-Ala was conjugated to various proteins, e.g. activated chymotrypsin, activated bovine serum albumin, oxidized ovalbumin, oxidized human IgG, and activated G-CSF. The proteins were activated at the carboxyl groups with EDC (carbodiimide) or N-hydroxy-5-norbornene-2,3-dicarboximide. Carbohydrate groups were oxidized with NaIO4 for activation. Extensive crosslinking of the proteins was prevented.

L21 ANSWER 18 OF 31 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 96094827 EMBASE
DN 1996094827
TI Synthesis of polyglutamine and dextran conjugates of streptomycin with an acid-sensitive **drug**-carrier linkage.
AU Coessens V.; Schacht E.; Domurado D.
CS Biomaterial/Polymer Research Group, Department of Organic Chemistry, University of Ghent, Krijgslaan 281,9000 Ghent, Belgium
SO Journal of Controlled Release, (1996) 38/2-3 (141-150).
ISSN: 0168-3659 CODEN: JCREEC
CY Netherlands
DT Journal; Article
FS 027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB A polymeric prodrug of streptomycin was prepared by coupling the **drug** via a spacer, glycine hydrazide, onto a polymeric carrier. In a first step, glycine N-Boc-hydrazide was linked to a 4-nitrophenyl chloroformate activated **polymer**. After removing the Boc group, streptomycin was coupled with the polymeric hydrazide with formation of a **hydrazone** bond. In order to target the **drug**-carrier derivative to the macrophages, 6-aminohexyl-.alpha.-D-mannopyranoside side groups were introduced. The polymeric streptomycin derivative was shown to be non hemolytic. The hydrolytic stability of the **polymer** -streptomycin conjugate was studied at physiological and lysosomal pH. Streptomycin release was found to be faster in the lysosomal pH range.

L21 ANSWER 4 OF 31 MEDLINE on STN
AN 2000095922 MEDLINE
DN 20095922 PubMed ID: 10632061
TI Acid-sensitive polyethylene glycol conjugates of doxorubicin: preparation, in vitro efficacy and intracellular distribution.
AU Rodrigues P C; Beyer U; Schumacher P; Roth T; Fiebig H H; Unger C; Messori L; Orioli P; Paper D H; Mulhaupt R; Kratz F
CS Tumor Biology Center, Department of Medical Oncology, Clinical Research, Freiburg, FRG.
SO BIOORGANIC AND MEDICINAL CHEMISTRY, (1999 Nov) 7 (11) 2517-24. Journal code: 9413298. ISSN: 0968-0896.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000214
AB Coupling anticancer drugs to synthetic polymers is a promising approach of enhancing the antitumor efficacy and reducing the side-effects of these agents. Doxorubicin maleimide derivatives containing an amide or acid-sensitive **hydrazone** linker were therefore coupled to alpha-methoxy-poly(ethylene glycol)-thiopropionic acid amide (MW 20000 Da), alpha,omega-bis-thiopropionic acid amide poly(ethylene glycol) (MW 20000 Da) or alpha-tert-butoxy-poly(ethylene glycol)-thiopropionic acid amide (MW 70000 Da) and the resulting polyethylene glycol (PEG) conjugates isolated through size-exclusion chromatography. The **polymer drug** derivatives were designed as to release doxorubicin inside the tumor cell by acid-cleavage of the **hydrazone** bond after uptake of the conjugate by endocytosis. The acid-sensitive PEG conjugates containing the carboxylic **hydrazone** bonds exhibited in vitro activity against human BXF T24 bladder carcinoma and LXFL 529L lung cancer cells with IC70 values in the range 0.02-1.5 microm (cell culture assay: propidium iodide fluorescence or colony forming assay). In contrast, PEG doxorubicin conjugates containing an amide bond between the **drug** and the **polymer** showed no in vitro activity. Fluorescence microscopy studies in LXFL 529 lung cancer cells revealed that free doxorubicin accumulates in the cell nucleus whereas doxorubicin of the acid-sensitive PEG doxorubicin conjugates is primarily localized in the cytoplasm. Nevertheless, the acid-sensitive PEG doxorubicin conjugates retain their ability to bind to calf thymus DNA as shown by fluorescence and visible spectroscopy studies. Results regarding the effect of an acid-sensitive PEG conjugate of molecular weight 20000 in the chorioallantoic membrane (CAM) assay indicate that this conjugate is significantly less embryotoxic than free doxorubicin although antiangiogenic effects were not observed.

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:141038 CAPLUS
DN 132:325978
TI Self-Cleaving **Ortho Ester** Lipids: A New Class of pH-Vulnerable Amphiphiles
AU Zhu, Ji; Munn, Robert J.; Nantz, Michael H.
CS Departments of Chemistry and Pathology, University of California, Davis, CA, 95616, USA
SO Journal of the American Chemical Society (2000), 122(11), 2645-2646
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB The potential of liposomes to function as carriers of pharmaceutical agents, and more recently, as vehicles for polynucleotide delivery, continues to stimulate the development of more effective lipid-based delivery systems. A principal area of liposome research has been the design of the "trigger" for the liposome to release its payload. Here, the authors engineered an **ortho ester** construct to effect lipid headgroup cleavage in response to mild acid-induced hydrolysis. When the **ortho ester** lipids are formulated into liposome aggregates, the tandem sequence of **ortho ester** hydrolysis and headgroup cleavage triggers liposome rupture and release of entrapped contents. These observations illustrate the potential in using **ortho ester** lipids for pH-mediated release of a liposome payload. Moreover, the acute sensitivity of the **ortho ester** linkage to hydrolysis at pH 4.5 falls within the acidification range of **endosomes** and points toward cellular delivery applications that proceed via endocytosis. Thus, the present approach to pH-triggered liposome disassembly provides a new tactic for the delivery of pharmaceutical agents.